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Hemorrhagic diathesis associated with obstructive jaundice

Jack Wickstrom

University of Nebraska Medical Center

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HEMORRHAGIC DIATHESIS ASSOCIATED
WITH
OBSTRUCTIVE JAUNDICE

BY
JACK WICKSTROM

SENIOR THESIS
UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE
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INTRODUCTION

Within the past year the solution of another surgical complication has been witnessed; ever since the surgery of the biliary tract made possible the exploration of the common duct for obstructive jaundice, one of the major causes of death has been postoperative hemorrhage. (191) Despite the employment of a number of remedies that have been suggested for the control and prevention of such hemorrhages, bleeding has continued as one of the important causes of postoperative mortality in such operative procedures, and this diathesis of jaundiced patients to bleed has been a clinical enigma.

Although the incidence of serious hemorrhage is relatively low the gravity of the problem has been in the fact that its occurrence can not be predicted either clinically or by means of the common laboratory methods now available with any degree of accuracy. (188) With the clinical application of knowledge gained through experiments in physiology and the development of new and more accurate laboratory methods the problems of diagnosis and proper prophylaxis to a great extent are being completed.

HISTORY

The history of hemorrhagic diathesis is interesting both from the standpoint of its antiquity and the diversity of opinion as to its pathogenesis. Hippocrates (2) described hemorrhage associated with jaundice which developed in autumnal fever and stated that such hemorrhages were distinctly beneficial. Galen (2) also discussed hemorrhage in jaundice occurring in fever epidemics and offered the first hypothesis as to its etiology; that the "retundancy of yellow bile which is mixed up with the blood and heating it, is carried up to the head where it ruptures the vessels and hemorrhage results." In 1800 Cullen (60) mentioned the occurrence of purpura and hemorrhage from "various parts of the body" in patients with jaundice, and observed that following such hemorrhages the patient often died "in a state of apoplexy". During the nineteenth century continental, as well as early American writers, reported a number of cases of hemorrhage in jaundice. In 1850 Anderson(11), a practitioner of Boston described a series of fatal umbilical hemorrhages in newborns in which he found congenital atresia

of the common duct at the time of autopsy. His search of contemporary literature revealed five cases but none of the authors offered any explanation of the fatal hemorrhage. Anderson's hypothesis was that the reabsorption of the contents of the bowel deprived the blood of its fibrin and gave rise to "the condition known as purpura hemorrhagica". In 1849 Ferrall (79) described fatal hemorrhages from the stomach mucosa in a jaundiced patient, and ten years later Menneret (160) and later Matthieu (154) reported cases in which severe hemorrhage from the mucous membranes occurred in icteric patients. Griffith (89) of Montreal reported a series of cases in which a hemorrhagic diathesis was present in jaundiced babies. Reclus, in 1872, was the first to describe bleeding in a case of chronic jaundice resulting from a common duct stone. (196)

Although the first surgery on the biliary tract is reported by Thadichum (212) to have been performed by one Johannes Fabricus in 1618 when he removed gall stones from the gall bladder of a living subject. Fabricus Hildanus (114) referred to this operation in his "Surgical Observations" but it isn't clear

whether or not the operation was premortem. Petit (178) leaves no doubt in one's mind in his reports beginning in 1733. His discussion of gall bladder tumors and the sequence of biliary obstruction and the controversy raised by his writings, established him as the founder of gall bladder surgery. Neither Petit nor Thadichum who wrote about a century and a half later failed to evaluate the difficulties of gall bladder surgery except one; neither mentioned the tendency to bleed which today stands as one of the difficult and perplexing problems confronting the modern physician. Neither Bobbs (24) of Indianapolis who fathered the modern cholecystotomy nor Langenbuch (128) who is credited with the first cholecystectomy in 1882, refer to the dangers of post-operative hemorrhage. Greg Smith was the first to remark on the bleeding tendency associated with jaundice as a surgical problem. This was in 1891 in his textbook on surgery. (212) Since then the material which has been written on the bleeding tendency in jaundice has been voluminous and the theories expounded as to its etiology equally as numerous and as diversified.

INCIDENCE

It has been pointed out above that the frequency of hemorrhage in jaundiced patients is not extremely high. (188) Nevertheless hemorrhage does constitute the most serious and by far the most frequent complication following operation on the common duct obstruction. (193) Petren (179) states that after operation for the relief of obstructive jaundice, hemorrhage may occur independent of age, sex, and the nature of the operation performed or of the agent responsible for the block in the extra hepatic bile system. Spontaneous hemorrhages from the mucous membranes of the body openings, from the gastro-intestinal tract and as purpuria is of quite frequent occurrence and of considerable importance from the standpoint of differential diagnosis. In a very extensive statistical study of 810 jaundiced patients entering the Cook County Hospital over a 14 month period, McNealy Shapirao and Melnick (146) found that in 676 of these in which the jaundice was due to some hepatic or extrahepatic duct pathology, 19.6% of the

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patients gave a history of abnormal bleeding at the time they entered the hospital. Although the most common lesions associated with hemorrhage in jaundice is some obstruction of the common duct, either calculi or benign or malignant obstructive lesions in the duct or at the head of the pancreas, hemorrhage occurs quite frequently in catarrhal jaundice (241, 146) is a common cause of death in congenital atresia of the common duct (10, 159) in metastatic malignancies and in cirrhosis of the liver. (146)

Ravdin (193) reported postoperative hemorrhage occurring in 20% of jaundiced patients undergoing biliary tract surgery with a mortality from hemorrhage of about 38%. McNealy and his coworkers report an incidence of 58% postoperative hemorrhage in patients that received no preoperative medication as controls in his experiments on viosterol and hemorrhage in jaundice. Several of the statistical studies which included cases from the last of the nineteenth century (21) (232) show that peritonitis was the most common complication of surgery on the biliary tract, but the more recent studies (30) (32) (112) show that hemorrhage is by far the most common postoperative complication in such surgery.

Hemorrhage is most commonly encountered in patients with jaundice of long duration, (14) (156) Kehr (117) reports a case, however, that hemorrhaged following surgery for the relief of obstructive jaundice which had been present but five days. In an analysis of cases coming to surgery for relief of biliary obstruction Ravdin (191) reports the incidence of postoperative bleeding was directly proportional to the duration of the jaundice; increasing from 13% in patients with jaundice of one weeks duration, to 71% in patients with jaundice of 36 weeks or over. Boyce (32) has found a similar correlation between duration of jaundice and the tendency to bleed and Petren (179) found that of 58 patients who died of hemorrhage after operation on the biliary tract for the relief of obstructive jaundice in Swedish Hospitals, in only eight instances was the icterus of less than three weeks duration. This may account for the increased tendency of patients to hemorrhage with biliary obstruction when the obstructing mechanism is due to malignancy of the bile duct, or its opening, over that which is present in patients with stones or stricture interrupting the bile ducts. (156) (14) (110) (183)

The importance of considering bleeding in jaundice in the differential diagnosis of gastro-intestinal lesions was brought out by Eusterman (77) who found occult blood in the stools of 20% of his patients with chronic cholecystitis and in 43% of the gastrics on these patients. He accounts for 50-60% of these on the basis of a bleeding tendency. Various men have reported series of cases in which cases of cholecystitis or common duct stone have shown hematemesis or melena as their chief complaint and the proper diagnosis was not made in most of these because of this. (133, 45, 231 82) DeCourcy (70) and others report cases in which gastro-intestinal bleeding has been cured by removal of a common duct stone or cholecystectomy. (246)

PATHOGENESIS

Numerous theories as to the pathogenesis or etiology of the hemorrhagic diathesis in patients with obstructive jaundice have been expounded during the past 150 years. Many theories that have been advanced had no factual foundation but were merely the individual authors own hypothesis. (2) (11)

Rohig probably laid the foundation for the first of ~~many~~ theories concerning the bleeding tendency in jaundice when he theorized that the circulating bile salts taurocholate and glycocholate caused the bradycardia and lowered blood pressure in jaundice. This apparently led to the later theory my Morawitz and Bierich (162) that the bile salts per se caused the bleeding tendency in jaundice. This was followed in 1909 by the work of King and Stewart (120) who corroborated the findings of Morawitz and Bierich. King and Stewart on finding the blood calcium decreased in dogs with bile duct obstruction, suggested that calcium combined with bile pigment in obstructive jaundice to render the pigment less toxic. King, Biglow and Pearce (119) later substantiated this change

in the blood calcium in dogs with biliary obstruction, but believe that the combination of bile pigment and calcium made the latter less available for the clotting process, and accounted for the delay in coagulation and hemorrhage of jaundice patients in this manner.

More recently Cantrow, Dodek and Gordon (50) believe that a deficiency of calcium exists in obstructive jaundice due to the increased amount of bile pigment in the blood and tissues but were unable to demonstrate any quantitative diminution in the blood calcium. Snell found that in dogs with common bile duct obstruction the calcium content of the serum did not vary from the normal. (217) Buchbinder and Kern (43) (44) have reported low calcium values in three cases of clinical jaundice and in puppies with obstruction of the common duct. Kirk and King (121) have found that whereas the normal diffusible portion of the blood calcium is 72.3% of the blood calcium, this figure may be reduced to 55.2% in jaundice; however, they have found similar changes in conditions which showed no disturbance of coagulation. Vines (229) in 1921

found that it is the calcium in the combined state rather than the ionized diffusible state which is necessary for the beginning of normal blood clotting. If the work of King and Stewart, and of King and Biglow and Pearce is considered in light of Vines findings it would appear that the unionized portion of calcium would be increased since the diffusible portion of calcium is decreased, according to them, by union with bile salts and the clotting process should be accelerated, this is not the case. Disturbances of calcium associated with jaundice will be discussed more fully in a later section.

Of the bile components, the bile acids are the most toxic. However, King and Stewart (120) believe that the bile pigments are responsible for the toxic symptoms occasionally seen in jaundiced patients. Wangansteen does not agree with them and points out, logically, that if the bile pigments were so toxic for the organism in any degree, all patients would show manifestations of toxemia in conditions of prolonged jaundice, and the fact remains that patients may continue in good health in spite of prolonged biliary obstruction. (241)

Because of the toxic and hemolytic properties of bile acids and their ability to inhibit the coagulation of blood when added in sufficient quantities in vitro, the origin of the hemorrhagic diathesis in jaundice has been attributed to them. More than thirty years ago, however, Morawitz and Bierich (162) concluded from their experiments on the blood of dogs that it was unlikely that the bile acids were responsible for changes in the clotting time of patients with obstructive jaundice. They found that the addition of ox-bile and bile salts sufficient to inhibit coagulation were never found in such concentrations in the blood of patients with obstructive jaundice. Gustav Petren (180) corroborated these findings in his work on hospital patients with obstructive jaundice; however, he did find that less bile salts were required to inhibit coagulation of blood in vitro in some jaundiced patients than in patients without jaundice, this was not a constant finding. Wildegrans (248) anastomosed the common bile duct to the vena cava in a number of dogs and although all died within a few days he was unable to show a delay in co-

agulation of the blood in any of them. Wangensteen has pointed out (238 - 239) that the excretion of bile acids is diminished following prolonged exclusion of bile from the intestine. This decrease in bile acid formation occurs when bile is lost from the body in the presence of a complete external biliary fistula, as well as when the bile escapes into the peritoneal cavity following severance of the common duct after prolonged occlusion of the duct. Apparently bile acid synthesis is interfered with. Brakefield and Schmidt (36) studied the excretion of the bile exponents in dogs with obstruction of the choledachus and found a gradual decrease of bile acids in the urine. Snell, Greene and Rountree (217) have made similar studies and found that the bile acids in the blood of their experimental animals with common duct obstruction were markedly increased during the second and third day but fell during the second week of observation; after that, the bile acids in the blood approached the normal levels. They concluded that a decreased synthesis of bile acids by the liver occurred following prolonged biliary obstruction. These findings have been corroborated in work on patients with hepatic disease by Rountree, Greene and Aldrich. (201)

The fact that the process of coagulation could be accelerated by use of calcium salts had been known for a considerable time by physiologists as Hammersten, Ringer and Green (251) before Wright applied this knowledge both clinically and experimentally and recommended the use of calcium chloride in conditions of delayed coagulation in 1891 (251). Mayo-Robison (156) was the first to suggest its use in the treatment of the bleeding tendency in jaundice. Its apparent success in controlling bleeding in a certain percentage of these patients together with the work of King and Stewart (120) and Marowitz and Bierich (162) already referred to, led to the hypothesis that a deficiency in blood calcium, either of the diffusible or nondiffusible fraction, was the factor resulting the delay in coagulation and the hemorrhagic tendency in jaundiced patients. There is considerable evidence, both clinically and experimentally that an actual disturbance in calcium metabolism does occur in obstructive jaundice. A number of years ago Pawlow (176) noticed that dogs with a complete biliary fistula developed osteoporosis. Seidel (206) *if* noted similar changes in patients and biliary fistula. The loss of calcium from the body depots and the

inability to assimilate fat has been described by Duttman (74) as the cause for osteoparotic changes in bone in cases with biliary fistula. A similar loss of calcium is said to occur in obstructive jaundice (147) and fat excretion in the stools is common knowledge. King, Bigelow and Pearce (119) found markedly lowered calcium values in the bones of dogs with obstructive jaundice and McGrudden (141) has noted osteoparotic changes in patients with long continued obstructive jaundice.

Walters and Bowler (237) noted that after the intravenous injection of a given dose of calcium chloride in jaundiced dogs, only half the increase in blood calcium occurs that is seen following the same injection in a normal dog. The lethal dose of calcium chloride was found to be greater for jaundiced dogs than for normal animals.

Cantrow, Dodek and Gordon, (50) following the experimental work of Kattman and Pidsky (115), Simpson and Rasmussen (208) and their own (85) experiments on the effect of parathyroid extract on coagulation time in patients with normal coagulation time, injected parathyroid extract in fourteen cases of jaundice with normal coagulation time and found a response the

same as in non-jaundice patients. Zimmerman (254) in similar experiments on dogs, jaundiced patients, and non-jaundiced patients found no change in the coagulation time of the blood in any group tested.

Lee and Vincent (129) state that the "calcium in vitro" test in which the venous blood from jaundiced patients can be made to clot more rapidly by adding calcium demonstrates that there must be a deficiency of available calcium in obstructive jaundice. Morawitz and Bierich have shown that by adding tissue extracts the blood of jaundiced patients could be made to coagulate three times as rapidly. (161)

Buchbinder and Kern (44) reported low serum calcium values in cases of clinical jaundice and puppies with common duct obstruction. Gunther and Greenberg (90) concluded however, that neither ionized nor non-ionized calcium is deficient in the serum of patients with common duct obstruction unless there is an associated serum protein deficiency and then only the non-ionized calcium level is disturbed.

Ravdin and his associates (193) conclude that in children as in puppies a low calcium level frequently accompanies jaundice and that the serum calcium is also frequently lowered in the presence of

hypoproteinuria, but that hypoproteinuria is rare in adult patients with obstructive jaundice.

The chemical evidence seems to be that calcium deficiency, if it exists in obstructive jaundice, is not of sufficient degree to be reflected in the serum calcium either total or diffusible (216) (51) (163) (50) (254) (135) (124) or our present methods are not sufficiently adequate to demonstrate this change in the blood. The chemical evidence of adequate serum calcium is corroborated by the physiological evidence, for the absence of neuromuscular hyperirritability in jaundice indicates a physiologically adequate blood calcium. (86) Furthermore, a calcium deficiency would be expected to hasten the appearance and increase the severity of tetany in a parathyroid-ectomized jaundiced animal, whereas, in reality it has the reverse effect. (44)

It has been proposed that it is the non-diffusible calcium which figures in blood coagulation (229). Stewart and Percival (224) and Kirk and King (121) contend that this fraction is decreased in obstructive jaundice. This fraction is low, however, in nephrosis (137) and parathyroid deficiency (95) (94) (197) but

neither the former (20) nor the latter is associated with a hemorrhagic tendency.

A deficiency of calcium in the circulating blood of patients with obstructive jaundice cannot be inferred because the administration of calcium chloride lowers the extravascular clotting time of the blood. Wangensteen points out that most investigators have observed a similar reduction in coagulation time in normal persons following calcium administration. It is also known that a number of other remedies injected into the organism produce the same effect. Among these hemostatic agents are gelatin (25) (253) (15), human serum and ox bile serum (244) (183) (157); extracts of blood lipoids and platelets, (80); roentgen radiation of spleen (222) (202) and other organs (165) (81); hypertonic saline (227) hypertonic glucose (118) (205) and eufhyelin (167) to name but a few. The shortening of the time in which blood clots, following the successful employment of a certain agent to arrest hemorrhage, does not necessarily indicate a deficiency in the organism of the remedy used. This applies as well to calcium. (241)

We must conclude that in light of our present

knowledge, a disturbance of calcium per se does not offer an explanation for the bleeding tendency as found in obstructive jaundice. (86) (254) (193)

Although several early writers have inferred that a deficiency of fibrinogen was one of the factors if not the factor in jaundiced patients which gave rise to the bleeding tendency. Doyon and his co-workers were the first to report a deficiency in fibrinogen as the probable cause of delayed coagulation of the blood in dogs in which liver damage had been produced by various measures. (71) (72) Foster and Whipple (81) in a study of blood fibrin corroborated the opinion of Doyon (13) that the liver extirpation removes the liver removes the only potential source of fibrinogen in the body. Later experiments on dogs by Williamson Heck and Mann (24) however, led them to conclude that the liver is not necessary for regeneration of fibrinogen. These experiments on fibrinogen in liver damage or extirpation led some investigators to suppose that during obstructive jaundice some deficiency of available fibrinogen might exist. In a study of the blood in jaundiced patients Lewisohn (131) concluded that there was a deficiency in fibrinogen as well as a decrease in prothrombin and an increase in

antiprothrombin in those patients with an increased risk of hemorrhage. Johnson (106) had concluded that clotting was delayed in experimental obstructive jaundice because the quantity as well as the quality of the fibrinogen and fibrin seemed deficient. In an extensive experiment on dogs, Moss (164) was not able to show any correlation between the fibrinogen content of the blood, the degree of icterus and the coagulation of the blood in obstructive jaundice and showed that fibrinogen is not decreased in experimental obstructive jaundice, in fact, Moss found that in acute obstructive jaundice the fibrinogen content was increased due to irritation of the liver parenchyma by the retained bile. These findings also corroborated the contention of Peters and Van Slyke (177) that a decrease of fibrogen does not parallel the degree of liver damage; in general Moss found the fibrogen content increased with liver destruction. These findings have since been confirmed by Ravdin, Riegel and Morrison (195) Cowan and Wright (58) and others (135) (136) These workers generally agree that the degree of liver damage necessary to produce a fall in the fibrogen level is greater than that found in simple obstructive jaundice and

that the bleeding tendency in jaundice can not be accounted for by fibrinogen deficiency.

The incoagulability of the blood in experimental animals following mesenteric vein injections of atropine, ox-bile, bile salts, chloroform, et cetera and the failure to elicit this alteration in clotting after systemic vein and artery injection would seem indicate that some anti-coagulant is liberated following liver injury. Doyon (71) carried out further experiments to confirm these findings and found that by profusing a removed dog's liver with saline anti-coagulable properties were imparted to the profusion liquid. He also found that if the blood from a normal dog was profused through such a liver the blood became incoagulable. Doyon has been able to extract anti-coagulant substances from other organs and has suggested that these substances are nucleo-proteins. (72) The work of Couradi (57) and of Boggs (25) substantiate his findings in part. The work of Lewisohn (131) referred to above, showed that an increase in anti-prothrombin is associated with an increased risk of hemorrhage in jaundiced patients. This had previously been suggested by Howell (100) (102). Moss (164) concluded, however, that

heparin or antiprothrombin as a cause of hemorrhage in jaundice is not substantiated by clinical or experimental proof. The quantity of heparin in the circulating blood is so small that its accurate estimation is impossible; however, the destruction of hepatic parenchyma by retained bile may possibly give rise to an increase of heparin in the blood in obstructive jaundice. (164)

More recently, Carr and Foote (51) have suggested that the retention of certain protein compounds in obstructive jaundice accounts for the apparent changes in the clotting mechanism and the tendency to hemorrhage is directly related to these retained compounds. They have claimed that "taurine and cystine and related organic sulfur products are the protein products which mostly back up in the blood and collect in sufficient concentration in the circulating plasma, to cause changes in the clotting mechanism". These intermediate products of protein metabolism influence the coagulation process in such a manner that the clot which forms as rapidly as normal is a non-retractile friable jelly instead of a strong occluding mesh. These investigators together with Naffziger (166) have claimed that in dogs with experimental obstructive

jaundice they were able to demonstrate an increased production of Bromphenylmercapturic acid over normal dogs. Abderhalden and Werthmeir (1) have substantiated their findings in part and Andrews (12) is of the opinion that there is a possibility of an effect on the clotting mechanism may result through the effect of sulphur compounds on blood calcium. It has been known for some time the presence of calcium and lead greatly increases the degree of deamination of cystine, an effect which suggests the precipitation by these metals of some intermediate substance which protects the amino acids from deamination. It is possible that some sulfur compound derived from cysteine or cysteine is capable of precipitating part of the serum calcium or more likely rendering it incapable of taking part in the clotting mechanism. This suggestion is advanced purely on a chemical basis. (12) Ravdin, Riegel and Morrison (195) have not been able to duplicate the findings of Carr and Foote, however, and do not agree with the chemical evidence presented by them for the role of cysteine in the bleeding tendency of obstructive jaundice. Boyce (29) has not been able to duplicate

these findings in experiments or in jaundiced patients and states that there does not appear to be sufficient quantitative distinction between the amount of Bromphenylmercapturic acid produced by jaundiced dogs and that produced by normal dogs under the same experimental conditions. One would hesitate to accept the theory of Carr and Foot in view of the lack of confirmation of their findings by other investigators.

The most recent work that has been carried out, both experimentally and clinically, on the pathogenesis of the bleeding tendency in obstructive jaundice have been prompted by reports in the literature on the subject of the "Koagulations Vitamine" and its relation to a hemorrhagic deficiency disease in chicks, Henrik Dam of Copenhagen and his coworkers (62,63,64, 65,66) were able to demonstrate that internal, subcutaneous and intramuscular hemorrhages developed in chicks which are on a diet deficient in certain fat soluble compounds but adequate in respects to vitamin A, B, B₂, C and D and in total fat and cholesterol. By substituting various foods to the deficient diets the hemorrhagic disease could be prevented or

corrected. After investigating numerous substances, Dam demonstrated that this essential antihemorrhagic factor was present in appreciable amounts in hog-liver fat, alfalfa, spinach, cabbage, and other leafy vegetables as an unsaponifiable, non-sterol fraction. Dam suggested that this essential factor be named vitamin K ("Koagulations Vitamine" in Scandanavian and German languages).

The ability of this anti-hemorrhagic factor to prevent or correct hemorrhage in chicks led to investigations as to the mechanism involved and Schonheyder (203) (204) demonstrated that in chicks the deficiency in vitamin K resulting in hemorrhage was associated with, and probably due to, a decrease in the amount of prothrombin in the blood. Together with Dam and Tage-Hansen (69) he showed that in normal chicks the prothrombin can be precipitated by the acetone method of Howell or the acetic acid method of Mellanby but that no such precipitate can be obtained from the plasma of K-avitaminous chicks. The work on this antihemorrhagic factor was later but independently taken up by Holst and Halbrook (98) and Almquist and Stakstad. (3) (4) (6) (8) (9)

Roderick (199)
200, investigating the hemorrhagic

disease of cattle that develops in animals fed spoiled sweet clover hay was able to demonstrate a deficiency in prothrombin in such animals; later, Quick (187) substantiated his findings. This condition in cattle is relieved by transfusion of blood and by feeding alfalfa which is protective in as low concentration as 5% of the total diet. Quick concluded that some toxic factor present in spoiled sweet clover hay depleted the supply of prothrombin and that an exogenous supply of some unknown substance present in whole alfalfa was required for its repletion. Just how spoiled sweet clover hay affects the normal store of prothrombin is not known; however, Roderick demonstrated focal necrosis of the liver in some animals dying from toxic sweet clover disease, and suggested the possibility that damage to the hepatic parenchyma may be the important factor. This possibility is supported by the recently published work of Smith, Warner and Brinkhous (213) at the University of Iowa who showed that in experimental chloroform intoxication in dogs a deficiency of both fibrinogen and prothrombin occurred and by varying the dose of chloroform, a deficiency in the prothrombin alone could be produced.

Their conclusions were that the hepatic parenchyma is concerned in the manufacture of prothrombin and that in dogs liver damage results in a decrease or arrest of this process of prothrombin production.

Hawkins and Whipple (93) were able to demonstrate a deficiency of "something needed for normal coagulation" in dogs with an external biliary fistula which manifested itself first as a delayed coagulation time and second as spontaneous bleeding from the mucous membranes and from trivial injuries. They also found that if the animals were fed bile the bleeding tendency could be corrected but that if the animals were bled to produce an anemia the amount of bile fed had to be increased or the dog bled spontaneously. Hawkins and Brinkhouse (92) later reported that in repeating these experiments they were able to demonstrate a marked prothrombin deficiency in the bile fistula dogs that bled. They found that the other clotting factors, fibrinogen, calcium, blood platelets, and antithrombin did not vary from their normal levels significantly. The relation of the decreased prothrombin and vitamin K in these dogs is obvious, since bile acids are necessary for the normal absorption

of fats and sterols from the intestine. Heyman (97) and Greaves and Schmidt (87) have demonstrated this fact recently when they showed that viosterol was not absorbed from the intestine after experimental ligation of the common duct or in bile fistula rats.

These demonstrable changes in the amount of prothrombin present in the blood in these various hemorrhagic states in lower animals led Quick to extend his investigation of prothrombin deficiency to include problems in blood coagulation in man such as hemophilia, obstructive jaundice, etc. In 1935 Quick and his coworkers (185) reported that a prothrombin deficiency was present in the hemorrhagic diathesis of obstructive jaundice. Quick cited evidence to prove that in the presence of biliary obstruction the only substance lacking for proper coagulation of blood was prothrombin and that fibrinogen, calcium and thromboplastin were all present in normal quantities in the blood of jaundiced patients. These authors presented a method of demonstrating this deficiency of prothrombin by adding optimal amounts of thromboplastin to recalcified plasma, leaving prothrombin as the only variable and recording

the coagulation time. Lewisohn previously had reported a deficiency of prothrombin associated with the bleeding tendency of obstructive jaundice but his hematological methods were not accepted and his work went unrecognized for the most part.

Smith and his coworkers (214), the group at the Mayo Clinic (148) (215) and Boyce (32) have all corroborated Quick's observation of a deficiency in the prothrombin content of plasma in cases of obstructive jaundice, especially if the hemorrhagic state developed. Both these groups of investigators independently conducted clinical experiments with vitamin K therapy in jaundiced patients and patients with biliary fistula and both groups reported that when concentrates of vitamin K together with human bile obtained from a fistula or animal bile salts were administered a marked decrease in the prothrombin time of the blood of patients who had jaundice or biliary fistula occurred and in some incidences the administration of these products had an inhibitory effect on actual bleeding. (47) These findings have been substantiated by Dam and Clavind (67).

Although the exact chemical nature of this new antihemorrhagic factor or the part it plays in prothrombin formation is not known, many interesting facts relative to vitamin K have been reported during the past year. The so called vitamin K is present as the non-sterols unsaponifiable fat-soluble fraction of ether extractions from alfalfa and a number of other compounds discussed below. As to the chemical nature of the material, little is actually known but Almquist and his coworkers (3) (4) (5) (9) have isolated a highly purified crystalline fragment which is potent in antihemorrhagic factors. In its purest form this crystalline substance is non-nitrogenous; contains no indol grouping, no phosphorous and no sulfur. It does appear to have one or more benzene nuclei; it is alkali labile but fairly heat stabile but is not particularly stabile to the general chemical procedures. Apparently it is optically inactive and has a molecular weight of about 600. Ultraviolet light and absorption materials such as aluminium oxide and magnesium oxide destroy its activity. Doisy of St. Louis (226) has done similar work and

it is likely that considerably more knowledge will be gained concerning the chemical and physiological properties and actions of this substance and the part it plays in prothrombin formation. Dam (64) has shown that vitamin K can not be identified with Vitamin A or D₁ because large amounts of these vitamins are ineffective in preventing the hemorrhagic disease in chicks. It does resemble vitamin E with respect to solubility and resistance to heating in air but is different from Vitamin E because large quantities of wheat germ oil do not afford protection against this disease in chicks. Dam and Glavind (66) have found that vitamin K is abundant in leaves of chestnut tree, spinach, cabbage, cauliflower, alfalfa, nettles, hemp seed, and a number of other leafy plants and as mentioned above, in certain animal products, namely, hog liver oil, and egg yolk. Subsequently, Almquist (7) has found that by fermentation of certain products (fish meal and alfalfa meal) from which vitamin K had already been extracted by ether and petroleum solvents, considerable quantities of vitamin K were synthesised by bacteria. This has been confirmed by work at the

Mayo Clinic (173). Certain animals, rats, guinea-pigs, dogs and probably human beings can dispense with vitamin K as such in their normal diets because of this bacterial synthesis of the vitamin which apparently takes place in their intestine. (203)

According to the evidence provided by the experimental work of Snell and his associates (215) and Brinkhouse (37) the prothrombin deficiency in obstructive jaundice is due to a failure to absorb or a failure to utilize the fat-soluble antihemorrhagic factor normally present in the diet which requires bile for its absorption. The necessity of having bile salts present in the intestinal tract for proper absorption of fat-soluble substances was demonstrated by Heymann (97) and Greave and Schmidt (87,88) in working with viosterol and later by Hawkins and Brinkhouse (92) in working with vitamin K and bile fistula dogs. In fact, Brinkhouse and his coworkers (39) have shown that the prothrombin level of the blood can be raised and the bleeding tendency controlled by feeding bile or bile salts alone to the patients with obstructive jaundice that are on a normal adequate diet. This has been

substantiated by Wangansteen (211), Ravdin (191) and others. The time required for raising the prothrombin level and controlling hemorrhage by feeding bile alone is often too long and for that reason is not satisfactory in the average case that comes to surgery. (37) (214) Quick (188) has suggested that the low fat, low roughage diet that patients with biliary disease are usually fed may also be an important factor in producing the K-vitaminosis present in those that hemorrhage.

The inability or failure to utilize the normal amounts of the vitamin absorbed from the gastrointestinal tract suggests that we may be dealing with an additional factor, liver damage. As has been mentioned previously, Roderick (199) investigating spoiled sweet clover disease in cattle and Smith and his associates (213) working with dogs and chloroform intoxication have shown that in both these conditions a decrease in prothrombin and actual hemorrhage are associated with demonstrable liver damage. Similar pathological changes are observed in the liver in both experimental and clinical obstructive jaundice, they are discussed more fully under pathology in a later section. In considering

the fact that liver damage does occur in obstructive jaundice and may be severe and extensive and that the formation of prothrombin is intimately associated with normal liver function (213) (188); it is easy to understand the fact that large doses of vitamin K and bile must be administered to stimulate or furnish material for prothrombopoiesis in the damaged liver. Liver damage, may also explain the rapid depletion of prothrombin in the blood of these patients (47) for Brinkhouse (92) and his associates have shown that in normal animals (dogs) bled sufficiently to produce a marked deficiency of prothrombin, the prothrombin level was restored to near normal within six hours.

The fact that normal animals have considerably more prothrombin in the circulating plasma than is necessary for the normal clotting process has been shown with the development of newer methods of quantitative prothrombin estimation. In chickens hemorrhage did not occur until the prothrombin had dropped below 20%; in cattle only when prothrombin fell below 10%; in rabbits when 95% of prothrombin had been depleted, and in dogs when 90% had been depleted.

Various investigators (37) (91) (188) (214) have agreed that from a practical standpoint, bleeding in jaundice does not occur until the level of prothrombin reaches a point below 20%, and conversely, as long as the prothrombin level remains above 20% no prolonged clotting time is demonstrable. This would explain why the jaundiced patient who has an apparently normal clotting time suddenly and unpredictably begins to bleed following an operation, although the amount of blood lost at operation has not been great. It would indicate that at the beginning there was a reduced amount of prothrombin which fell to 20% or less of the amount normally present, possibly as the result of even a small loss of blood or operative trauma to liver or hepatic damage from the anaesthesia. (145) (148) (193) (241)

This decrease in prothrombin which results from liver damage confirms in part the contention of many surgeons and experimental investigators that bleeding tendency in jaundice is the result of liver damage and that alone. (71, 73, 146, 190, 217, 235, 241) Although the exact mechanism involved is still not definitely established this fact is brought out in many cases of liver damage without jaundice, cirrhosis

chronic cholecystitis, phosphorous or chloroform poisoning, and acute yellow atrophy of the liver all exhibiting hemorrhage in some degree quite frequently. (75) (146) Ravdin, (195) Quick (188) and others (33) (220) have shown that in many patients that exhibited a hemorrhagic diathesis a markedly defective liver function was present. Boyce does not accept the absolute cause and effect relationship between liver damage and hemorrhagic diathesis because in a number of cases with marked tendency to bleed the liver function (29) (30) using Quick's own test (184) (186) was normal or approximately so. The weight of collective opinion however (104) (145) (173) (110) (193) (236) (241) seems to be that if there is not a definite cause and effect relationship between liver damage and the hemorrhagic diathesis the relationship is so close that for practical consideration it may be accepted as such.

Another purely mechanical factor in producing postoperative hemorrhage in jaundiced patients has been suggested by Ravdin and Frazier (192) in their experiments on intrahepatic pressure in biliary obstructive jaundice. They demonstrated that sudden

decompression by release of the ductal occlusion results in massive hyperemia of the sinusoids and extravasation of blood into the liver parenchyma. This has been suggested by other workers (123) as an important factor in hemorrhage following release of biliary obstruction, and gradual decompression of the biliary tract has been recommended by a number of surgeons. (123) (192)

PATHOLOGY

In obstructive jaundice, no matter what the obstructing agent is definite pathological changes occur in the biliary tract and liver parenchyma in varying degrees which explain the pathological physiology described above. According to MacMahon and Mallory (142) the liver in cases of obstructive jaundice is of normal size, the surface is smooth or finely granular and the entire organ is stained an intense green. The first change demonstrable microscopically is a proliferation of the epithelium of the bile ducts which show many mitotic figures; this may be attributed to the irritating action of the retained bile salts. The ends of the ducts are clubbed and varicosed. Because of the close parallel to the hydronephrosis seen in the kidney following urethral obstruction, the term of "hydrohepatosis" has been applied to this condition found in the liver following protracted complete obstruction of the bile ducts. (34) If infection is not present, the picture is that of hydrops of the entire biliary system in some degree.

The canaliculi are filled with biliary thrombi, especially near the central hepatic veins. Because of the tortuosity and elongation of the ducts they appear much more numerous than usual, but there is no formation of new ducts. The minute channels which pass into the liver cells are ruptured and there is disintegration and atrophy of parenchymal cells at the periphery of the so-called "hepatic" lobules. Eventually there is infiltration of lymphocytes and mononuclear cells along the ducts and the hepatic cells at the bases of the acini atrophy. A gradual progressive increase of the portal connective tissue then takes place. The ducts that were at first distended with inspissated bile gradually becomes filled with colorless mucus derived from the epithelial cells of the ducts. These cells also remove the bile pigment, causing the change in color. Eventually, if the process is not interrupted, the stage of advanced cirrhosis is reached. (111)

If, however, the presence of microorganisms complicates the picture, there is suppurative cholangitis with multiple hepatic abscesses around the terminal biliary ducts. The entire system of ducts

is filled with bile stained pus; the mucous membrane disappears leaving a sloughing submucosa, and the walls and portal spaces are infiltrated with polymorphonuclear leukocytes. (143) In the event the process becomes chronic, there is fibrosis of the walls of the ducts and later of all the portal spaces and lymphocytes infiltrate the submucosa, particularly around the parietal sacculi. This diffuse organic injury accounts for the inability of the liver to completely return to normal, in spite of surgical procedures aimed at establishing proper biliary drainage to ex^hance anatom^{ic} and physiological regeneration. It also furnishes definite evidence to substantiate the contention of many investigators that the degree of liver damage is directly proportional to the liability of these patients to hemorrhage whether on the basis of prothrombin regeneration or not. (104) (145) (188) (193)

In those patients that hemorrhage proves fatal, the hemorrhage is most frequently found at the operative site and produces an accumulation of blood in the peritoneal cavity. In cases of cholecystgastrostomy or choledachoduodenastomy bleeding

usually occurred into the anastomosed organs, and a soft clot is found obstructing the stoma at necropsy.

(26) In such cases the passage of bile into the intestine is prevented and a viscous circle produced since it is clear that little vitamin K can be absorbed under such circumstances. Bleeding may occur into the liver parenchyma and appear as hemorrhage from the T-tube or into the bowel. (26) (107) (127)

The hemorrhage site is often occluded by a loose friable non-retractile clot through which additional blood "oozes". This has been described by many surgeons (32) (51) (166) (195). The friability and non-retractability of the clot is due to the deficiency of prothrombin. Since the process of coagulation is one of mass action, the decreased amount of prothrombin results in a decreased amount of thrombin with a subsequent deficiency in the quantity and quality of fibrin produced. (188)

DIAGNOSIS

Much has been done in the past twenty years to aid in the diagnosis and control of hemorrhage in jaundiced patients. Better clinical understanding,

better laboratory methods for measuring clotting time, and tests for measuring hepatic disfunction have all added to the accuracy of predicting which jaundiced patients would bleed and which would not. Until recently, however, it would seem that the only way to determine a bleeding tendency accurately is to see if the patient bleeds, yet such a "posteriori determination" would be of no value in preparing the patient for operation. (104)

(55) Because of this numerous special tests have been devised for use as routine laboratory methods; for the most part they have been unsuccessful. Therefore, we will consider more fully only those which in light of our present day knowledge seem to be of considerable value and pass briefly over the others.

Clinical data alone is relied upon by many surgeons in determining a tendency to hemorrhage in jaundice and, if properly evaluated, is of greater value than are most laboratory tests which are commonly at the disposal of the surgeon. Both the degree of liver damage and the tendency to hemorrhage are greater when a patient is weak and debilitated, when submucous or subcutaneous hemorrhages

occur and when the jaundice is deep, increasing in depth and of long duration; far less so than when converse conditions occur. (56) Hepatic function is usually adequate and there is little danger of hemorrhage when jaundice following biliary colic and obstruction of the common duct is allowed to subside before operation. Danger from postoperative hemorrhage is greater when biliary colics become frequent or when partial or complete obstruction persists for so long that jaundice does not clear. Surgical interference can best be done when a decrease in the depth of jaundice occurs, as measured by the icterus index. Danger from hemorrhage is especially great when jaundice from chronic obstruction of common duct is of many weeks or months duration and is fixed or increasing in depth. In such cases a favorable time for surgical intervention can not be found therefore, it is best to explore the tract before further hepatic damage occurs and after proper adequate preoperative treatment. (56) (183) (241) The tendency to hemorrhage is greater in cases due to benign or malignant stricture than in cases due to stones in the common duct, because of greater

degree of liver damage (14) (56) (110) (156) (188) and the expected improvement is small if surgery is delayed. Again, the importance of carrying out an exploratory operation as soon as the jaundice is fixed, as soon as acute parenchyma damage has subsided and when preoperative preparation has accomplished as much as possible cannot be emphasized too strongly.

Although the depth of jaundice as measured by the icterus index is by no means accurate (86), it is used as a means of estimating the tendency of jaundiced patients to hemorrhage by some. (26) Comfort and Nygaard (56) state that in their experience they have found that the danger from hemorrhage in obstructive jaundice is relatively greater when the bilirubin in the blood is 20-25%, indicating severe hepatic damage, than when the bilirubinemia is decreased to the usual depth associated with obstructive jaundice from a common duct stone. (10-15 mg.%)

Of the common laboratory procedures frequently used in diagnosis or prediction of any latent bleeding tendency the coagulation time and bleeding time have been relied upon most extensively in the past. Many of the therapeutics measures that have been

proposed for use in jaundiced patients that bled abnormally have been based on their ability to shorten the coagulation time. The most accurate of the several methods in use is that of Lee and White, (129) (172) in which 1 cc. samples of freshly drawn venous blood are placed three test tubes 8 mm in diameter and the tubes are tipped in succession every 15 seconds; when the second tube can be tipped without the blood flowing, the time is recorded as the coagulation time. The normal is 5 to 8 minutes. It may also be determined roughly by placing a drop of blood in a watch glass and a needle passed through the drop every 30 seconds. When a thread of fibrin is picked up by the needle the blood is said to have clotted. The normal is 7 minutes or less. (172) The capillary tube method is commonly used, in which capillary tubing is filled with a drop of blood, successive pieces of tube broken off every 30 seconds after the first three minutes and the time interval measured from the time the drop appears on the skin surface until a fibrin thread can be stretched between the broken ends of the tube. The maximum normal coagulation time by this method is also 7

minutes. (122) Altogether there are over 35 methods for determining the coagulation time of the blood. (211) Solis-Cohen (211) has made an extensive study of coagulation time and concludes that interpretation is very difficult because of the various factors which affect the clotting time such as contact with air, mechanical disturbance of the blood, evaporation, temperature, dilution, end-point adopted, personal equation, contact with tissues, etc. Many writers have concluded that prolonged clotting time bears little or no relation to clinical bleeding and is often normal in severe blood dyscrasias. (22) (78) (103) (122) (125) It is only diagnostic in hemophilia in which a prolonged coagulation time is obtained. Ivy concludes that the coagulation time is of no value in determining a bleeding tendency in jaundice. (104) His opinion has been confirmed by Ravdin (195), Walters (233) and Colbeck (55).

In 1915 Lee and Vincent (130) published a "calcium in vitro" test for determining whether blood that showed a delayed clotting time could be made to clot more rapidly by adding three drops of 1% calcium chloride to 1 cc of blood. If the clotting time had been prolonged because of the presence of bile salts, ~~Lee~~ and Vincent claim this procedure

brings about a marked decrease of the clotting time, but in cases due to other causes the test is without effect. Morawitz and Bierich (162) however, have shown that tissue extracts will produce the same changes, and, although the test is still accredited in England (75), most investigators do not feel that it has a sound physiological basis or is substantiated clinically. (104)

Bancroft and his coworkers (17) devised a clotting index calculated from a composite of the determinations of the prothrombin content, fibrinogen content, platelet count, degree of platelet lysis and antithrombin. In later studies they dropped the platelet count and lysis because they could find no clinical correlation. They concluded that no one factor can be isolated as the cause of bleeding or clotting in any of the dyscrasias and that the most accurate determination of a bleeding tendency could be made only after operation. Mills (158) and Clute and Veal (153) believe that this method of determining coagulation time is too elaborate and that splitting up of such a process is misleading since in any one case one factor may compensate for another.

Nygaard and Baldes (168) (170) working at the Mayo Clinic on blood coagulation, devised a method of measuring coagulation of plasma by means of a photo-electric cell as a modification of Howell's (100) so-called prothrombin test. The method is based on the principle that increased absorption of light occurs during coagulation of the blood plasma. Variations in transmitted light are measured and recorded by means of a photoelectric cell which is connected to a sensitive galvanometer. The deflection of the galvanometer is reflected on a rotating photosensitive paper in a camera. This unit is termed the Baldes-Nygaard coagelgraph and the graphs obtained are termed coagelgrams. By this method the clotting process is undisturbed by motion of the tube; the personal element is eliminated, and the changes are recorded earlier and more accurately. The obvious disadvantage is the elaborate and expensive apparatus necessary for conducting the test.

Normal coagelgrams show three marked points of change. The first, when fibrin first appears (about three minutes); the second, when the clot is formed (about four to five minutes); and the third, when

the clot begins to express serum. Nygaard found that in obstructive jaundice a disturbance occurs in the process of coagulation as shown on the coagelgrams, the second phase shows no definite break, (169) that is, the fibrin does not form a clot as readily as normal. This he terms "flattening" of the coagelgram. Nygaard and his associates (56) have found an accurate correlation between clinical bleeding in jaundice and the so-called flattening of the coagelgram. In light of more recent findings (Quick's (185) prothrombin time, etc.) Nygaard's estimation of coagulation can be criticized in that it does not measure prothrombin directly but rather measures fibrin formation. The expensive and elaborate equipment necessary to conduct the test is a marked disadvantage also, and would prevent its general adaptation for general laboratory use. There are definite limitations on coagulation studies, furthermore, in that a daily variation is present normally and also in obstructive jaundiced patients and an improvement in the coagelgram with the patient under treatment may impart a false sense of security that the patient will not hemorrhage postoperatively. Ravdin, Riegel and Morrison have pointed out (194)

(195) furthermore, that patients with increased coagulation time are not necessarily the ones which hemorrhage.

Several years ago Linton (134) reported favorably on the use of the sedimentation rate in jaundiced patients as a means of determining a latent bleeding tendency. It was investigated by a number of workers and the general opinion is that it is of little or no value in predicting hemorrhagic diathesis in jaundiced patients. (51) (53) (54) (195)

In bleeding dyscrasias the simple fact is that the patient bleeds; the problem is to demonstrate beforehand that he is going to bleed. Wangensteen asks, "if the bleeding time doesn't measure a tendency to bleed, what does it measure?" Ivy (104) however, concludes that, for the most part, determination of the bleeding time has been disappointing in predicting latent bleeding tendency in jaundice and has been of little more value than the coagulation time. In severe anemias, febrile states, acute leukemias and in pronounced hemorrhagic diatheses in general the bleeding time is prolonged and it is probably the single best method of predicting a bleeding tendency in these conditions. Latent bleeding

tendencies, such as found in jaundice, is not revealed by simply puncturing the skin as in the most commonly used method, that of Duke, which has a normal of thirty seconds to three minutes. Ivy found that in his series of cases the Duke bleeding time was within normal limits in most jaundiced patients that hemorrhaged postoperatively. (104) McNealy Shapiro and Melnick report similar findings. (146)

For this reason, Ivy (104) attempted to devise some method by which jaundiced patients with a latent bleeding tendency could be made to bleed excessively from an ordinary skin puncture. One factor in bleeding which has received little attention is the "tonicity" of the capillaries (241) (104) In small vessels it is the retraction of their walls which stops bleeding to a large extent. Von Bermuth (230) and Magnus (149) have demonstrated this by actual observation of the capillaries with a capillary microscope. In cases of hemophilia, von Bermuth found that the capillaries did not contract after being cut, but remained patent and bled. No other factor can explain the fact that normal bleeding time (Duke) is much less than normal coagulation time.

Ivy modified the Duke bleeding time by placing a pressure cuff on the arm and applying 10 mm. of mercury pressure, sufficient to cut off effective venous return and thus overcome capillary tonus. Thus, he simulated the clinical situation when ether, shock, and operative trauma result in capillary paresis and bleeding. After a large series of normal patients had been tested the upper limits of normal for this bleeding time were established at 240 sec., and rarely did it go over 180 sec. In testing jaundiced patients Ivy found in many cases that although the Duke bleeding time was normal, the venous pressure bleeding time was definitely prolonged, and these cases with prolonged venous pressure bleeding time were almost always the ones that bled either spontaneously or after operation. (104)

McNealy Shapiro and Melnick tested the "Ivy" bleeding time in a series of 810 cases and concluded that it was the most effective method of predicting a hemorrhagic diathesis in obstructive jaundice or liver insufficiency and proved to be practically 98% efficient. (146) Bays (35) however, found that in thirty-five patients with obstructive jaundice

the nine that bled postoperatively showed an elevated Ivy bleeding time, but so did fifteen of the twenty-six patients who did not bleed. This seems a very high percentage of what might be called negative error. Boyce and McFetridge, (32) have investigated the accuracy of the Ivy bleeding time and criticized it because (1) the puncture is so small they question whether so small a clot is seriously affected by a limitation of venous return; and, (2) the upper limits of normal (four minutes) allows patients with a bleeding tendency to be included among normals. They also found that the venous pressure bleeding time tends to be low in younger persons and to become elevated in the aged. Boyce and McFetridge have found the Ivy bleeding time normal when the serum volume test (31) (to be discussed later) indicated a definite hemorrhagic tendency which was proved in one case that actually bled. The general consensus of opinion seems to be that the Ivy bleeding time is of definite value and easy to do and the proper evaluation will depend on further clinical application. (146) (37) (188)

Boyce and McFetridge (31) devised a simple test for the hemorrhagic diathesis in jaundice based

on the ability of a clot to express serum, which they have used extensively during the past two years. This serum volume test requires only a syringe and a graduated tube. An arbitrary amount of blood, preferably 3 cc, is collected and allowed to stand at room temperature for four hours. The clot is then removed and studied and the serum volume read. The index is determined by dividing the serum volume by one-half the volume of blood withdrawn. The standard of normal is one and indices below this level are progressively indicative of hemorrhage. A routine blood count is necessary to determine or demonstrate an anemia and the proper corrections made. When an anemia is present the serum volume will naturally be greater than one-half the blood volume.

In later publications (92) (29) these writers and others (145) have reported favorably on the accuracy of this test in predicting a latent bleeding tendency in obstructive jaundice. The test will probably require further application before its true value can be determined, however, but its simplicity and apparent accuracy, is warranting its adoption more generally than it is at the present time.

Probably the most accurate method yet devised for determining a latent bleeding tendency in patients with obstructive jaundice is a quantitative determination of the prothrombin level by one of various methods. Prothrombin is known only its ability to form thrombin; for this reason its quantitative estimation depends upon biological assay methods. Howell used the clotting time of recalcified plasma as a measure of prothrombin present. (100)

(102) Quick and his associates (85) have improved the method by adding tissue extracts to the plasma to insure complete and prompt conversion of all prothrombin present. Their test is based on the assumption that the blood clotting mechanism proceeds in two steps:

- (1) Prothrombin plus thromboplastin plus calcium equals thrombin.

- (2) Fibrinogen plus thrombin equals fibrin;

and that the rate of clotting is proportional to the concentration of thrombin. If the first phase proceeds according to the law of mass action, the rate of thrombin formation is a product of the concentration of prothrombin, thromboplastin and calcium. When oxalated plasma is used and recalcified

with the optimal amount of calcium (0.1 cc of 0.025 M calcium chloride added to 0.1 cc of plasma obtained by mixing 9 cc of whole blood with 1 cc of 0.1 M sodium oxalate) and an excess of thromboplastin is added (obtained from rabbits brains), only prothrombin is left as a variable and its concentration should determine the clotting time. The time necessary for the clot to form is inversely proportional to the amount of prothrombin present.

The workers at the University of Iowa (242) contend that this total clotting time, however, is made up of the prothrombin conversion time and of the time required for the thrombin formed to react with the fibrinogen. The conversion time alone depends in an obscure way upon the prothrombin concentration and upon other variables of unpredictable importance. The thrombin phase overlaps the conversion phase to a variable degree and is itself a complex function of the amount of thrombin formed. The uncontrolled product of these two reactions gives a clotting time which is very difficult to interpret in terms of prothrombin concentration. Because of this Smith and his

workers (242) have separated the two phases experimentally and use only the time required for the second phase as a measure of prothrombin. To do this, one can transform the prothrombin to thrombin in a preliminary step; then the thrombin formed may be titrated by means of serial dilution technic.

Although the so-called quantitative prothrombin determinations in any of their present forms are too complex for routine use in the average clinical laboratory, they do offer the most accurate means of determining which jaundiced patient will bleed and which will not bleed spontaneously or after surgery and with the adoption of a more simplified technique they will be used more universally. Quick (185) (188) warns that a patient with a decreased **prothrombin** level but still above the point at which hemorrhage occurs (usually 20%) should be rechecked following surgery and proper measures taken to insure correction of the prothrombin deficiency before active hemorrhage begins.

The use of liver function tests as a means of measuring the tendency to hemorrhage has received some mention in the literature (19) (33) (184) (186)

(188) (190) (220) and, although the exact value is not agreed upon any test which informs the clinician about the degree of hepatic damage informs him also about the tendency to hemorrhage. (56). Quick does not believe any patient showing 50% liver function by any of the tests should be allowed to go to surgery unless indications for surgery are urgent. (188). Suffice to say, any liver function test which shows marked hepatic damage indicates a more marked tendency to hemorrhage than when the hepatic damage is minimal. The work of Mann and his associates (150) (152) on liver function have shown that experimentally 10-20% normal liver tissue is sufficient to carry on normal hepatic activities. In many cases the degree of liver damage is not of sufficient degree to be revealed by liver function tests, (32) for this reason the accuracy of liver function tests in measuring the tendency of jaundiced patients to bleed is questioned.

TREATMENT

The treatment of the hemorrhagic diathesis associated with obstructive jaundice is, simply stated, the early relief of the biliary obstruction thus preventing further liver damage and diminution of liver function. (241) In most cases the surgeon does not have the opportunity to see the patient before some impairment of the liver has occurred and the probability of hemorrhage must be considered. The preparation of the jaundiced patient for operation includes all the precautionary and rehabilitative measures which should precede every major operation and in addition an attempt must be made to meet the added hazard of hemorrhage and liver damage associated so frequently with the symptom complex of jaundice. A considerable number of these additional measures employed to correct the bleeding tendency have been considered under the pathogenesis of the hemorrhagic diathesis. Only the more generally employed methods will be considered here with brief evaluation of their relative worth. Of special importance in preparing a patient

with some obstructive biliary lesion for surgery is bed rest in a hospital where more accurate diagnostic and therapeutic measures can be instituted; an adequate intake of food and fluid and control of pruritis can be insured. (56)

Wright (251) was the first to suggest the use of calcium as a hemostatic agent in conditions associated with a delayed coagulation time. In 1884 Mayo-Robison (156) recommended its use in obstructive jaundice, but it wasn't until 1921 when Whipple (254) and Waters (232) popularized the intra-⁸⁷venous use of calcium that its preoperative use became widespread in this country. The method recommended for administration was 10 cc of a 10% solution of calcium chloride each day for three days. (27) At the present time calcium gluconate is used more frequently because it is less irritating to the tissues and may be used intramuscularly. The amount of calcium furnished is the same. Some surgeons prefer peroral administration of calcium. Ivy has shown, however, that the absorption of calcium from the intestine depends on the presence of hydrochloric acid in the stomach; since patients with gall bladder disease may have an achlorhydria, the

peroral administration of calcium salts is questioned. (145) Many writers question the value of calcium therapy as a measure to control the bleeding tendency in jaundiced patients (146) (86) and Ravdin states that its preoperative use is not justified and he has abandoned its use except in children and in hypoproteinemia, (193) basing his opinion on the work of Grunther and Greenberg (90). The success of Walters (233) (234) and Judd, (108) in using calcium preoperatively however, can not be disregarded, and, although the physiological basis for calcium therapy is questioned it still must be considered of value as a hemostatic agent in jaundiced patients. (241)

The observations of Wright (252) that the coagulation time was decreased after ingestion of a meal and of Cannon and Gray that adrenalin caused a reduction in coagulation time by mobilizing the blood sugar formed the basis for the use of the high carbohydrate diet and intravenous glucose therapy in jaundiced patients to reduce the coagulation time and prevent bleeding. (175) Although Schreiber (205) and Kehr (118) advocated the use of hypertonic glucose solutions to control hemorrhage in jaundice and Mayo

(155) recommended its use with calcium in obstructive jaundice, it wasn't until 1930 that Ravdin and his coworkers (194) reported the effect of glucose alone on the coagulation time of the blood of jaundiced patients. Although there is much additional data in the literature to show that hyperglycemia is often associated with a reduction of clotting time no definite direct physiological relationship can be established between the blood sugar level and coagulability. (58) (194) (195) The work of Mann (151) (153) and Ravdin (189) (191) have clearly established the fact that a high carbohydrate intake improved liver function in obstructive jaundice and prevented further liver damage, and, by improving liver function, favorably affects coagulability of the blood, both experimentally and clinically.

Intravenous glucose should be given as an adjunct to a high carbohydrate diet both preoperatively and postoperatively until convalescence is definitely established. 3000 to 4000 cc 5% solution of glucose, properly buffered, is given every 24 hours. The urine should be checked to determine glycosuria. McNeally (145) has warned that glucose therapy should

not be delayed until the last minute and then "pushed" so vigorously that sugar spills in the urine. Luckens (140) suggests the use of insulin to insure better storage of glycogen in the liver. Several writers (56) have reported favorably on the use of intramuscular injections of liver extracts with the intravenous glucose to improve liver function and insure glycogen storage.

If a marked bleeding tendency is revealed by various diagnostic measures or there is a history of spontaneous hemorrhage, blood transfusions should be given once or twice before operation and again postoperatively if necessary. (145) (174) Recent studies suggest that the chief effect of transfusion is to elevate the level of prothrombin, but that this is only a transitory benefit since the body is apparently not replacing prothrombin. Hence, preoperative transfusion for prevention of postoperative hemorrhage may be open to serious question as to its benefit. Judd, Snell and Hoerner (114) have shown that transfusions are of extreme value in controlling hemorrhage in jaundiced individuals. Snell and MacLay (119) found that in hepatic insufficiency there was a

definite anoxic anoxia of liver cells evidenced by central cell atrophy in the liver labules. Judd and his coworkers (114) found that in obstructive jaundice the oxygen saturation varied from 9 to 20% volume percent with normal saturation varying from 79.8 to 95%. From these findings they concluded that a considerable portion of the beneficial effect of transfusions in these patients was due to the increased oxygen supply to the liver parenchyma and subsequent improvement of the liver function.

Vitamin therapy in patients with obstructive jaundice has been suggested by experimental work by Heymann and Greaves and Schmidt who showed that the absence of bile in the intestinal tract seriously interfered with the absorption of fat soluble vitamins. The liver stores vitamin D and apparently utilizes it in its hemostatic function. (41) Much work has been published recently demonstrating the profound effect of vitamins A and D on various blood coagulation factors (126) (138) (59). In particular, the effect of vitamin D in favorably altering these factors and in reducing bleeding and coagulation time

and bleeding tendency in various conditions has been frequently reported. (181) (126) (20) McNeally Sapiro and Melnick (146) in a study of 810 cases of jaundice entering the Cook County Hospital over a fourteen month period used viosterol in approximately two-thirds of the patients that showed a prolonged Ivy bleeding time. They reported very favorably on the results obtained in preventing such patients from hemorrhaging and suggested its use in every case of obstructive jaundice that shows a latent bleeding tendency. In general, the dose of viosterol used is thirty drops per day with some bile salt or whole bile preparation in the presence of acholic stools. Gray and Ivy (86) have shown that viosterol therapy in jaundiced had no con-
sistant appreciable effect on the blood calcium. 81
Smith and his associates (243) have reported that there was no appreciable change in the prothrombin level of experimental animals when placed on viosterol and bile salts. From their experimental work McNeally Shapiro and Melnick explained the success of vitamin D and Vitamin A therapy on the basis of improved liver function by correction of an apparent D-avitaminosis and concluded that viosterol and vitamin A are of

definite value in correcting the bleeding tendency in obstructive jaundice and insuring a normal post operative course if the degree of hepatic damage is not too great. Boys and Johnson (35) (105) have corroborated their findings in part.

Vitamin K. therapy has by this time become thoroughly established. (191) (29) (32) Its properties and apparent physiological action have been discussed under the pathogenesis and will not be reported here. Alfalfa has been used as the source of vitamin K concentrates by the majority of investigators since it is cheap, easy to handle, and no variable, such as bacterial action, is needed to extract the concentrate. (47) (32) (243) (4) The preparation used at the Mayo Clinic had a potency of 20 mg or less per kilogram of chick diet or measured by the prophylactic biologic chick method; (182) and 200 mg. of the crude concentrate is equivalent to approximately 66 grams of dry alfalfa meal, or approximately 37,500 Dam units. (203) This is approximately twenty times the calculated dose by weight for the average sized man. The question of exact dosage of vitamin K. still remains a difficult problem chiefly because the material is not

available in pure form and because in many instances the dosage varies with the individual case. In the preoperative treatment in patients who have jaundice, three types of patients may be considered: (1) those who have a normal prothrombin clotting time; (2) those who have an elevated prothrombin time, and (3) those who are actively bleeding. The first type needs prophylactic treatment and the condition of the remaining two types constitutes a potential or real emergency. For prophylactic use in cases of jaundice in which surgery is contemplated two to six gelatin capsules (each containing 200 mg. of alfalfa concentrate) and one to two grams of animal bile salts seem to be an adequate daily dose. In many cases of jaundice, administration of large quantities of bile salts alone, even when the patient is ingesting a good diet, will not alter highly elevated prothrombin clotting times and concentrates of vitamin K have to be given in addition to the bile salts to produce the desired effect. (47) (214)

The second and third groups of cases are a more serious problem. In certain cases of jaundice with obstruction to flow of bile and injury to the liver, a high "prothrombin clotting time" or even

bleeding may be encountered and then much larger doses of a vitamin K concentrate may be necessary. In such instances, two to four grams of bile salts and one to two grams of the concentrate of alfalfa are given in 250 cc to 500 cc of warm normal saline by duodenal tube or T-tube. In most cases the active bleeding can be controlled by this method but it may be necessary to repeat the procedure one or more times before the prothrombin time returns to a normal level or the bleeding is stopped; when such large doses are used the prothrombin time usually decreases within six to twelve hours. (47)

Dam and Glavind (67) have reported that the use of intramuscular concentrates of vitamin K was satisfactory but the decrease in prothrombin time occurred on the fifth to sixth day after injection. Butt, Snell, and Osterberg, (47) have reported that the intramuscular injection of vitamin K concentrate in peanut oil is not as effective in reducing the prothrombin time as the same quantity of material administered by mouth. The latest work on purified vitamin K concentrates in crystalline form (5) (236) may prove of great therapeutic value by affording a substance satisfactory for intramuscular and intravenous administration.

The findings of Quick (87) that an antihemorrhagic factor remained in alfalfa after extraction with ether, a process which should remove the vitamin K, and the more recently reported studies of Lichtman and Chambers (132) indicate that substances chemically different from the preparation of vitamin K now in use may also be effective in increasing coagulability of the blood. These findings in no way discredit the value of vitamin K as a therapeutic agent, but rather intimate the vast amount of research remaining to be done on the entire problem of antihemorrhagic substances and their relative therapeutic value.

PROGNOSIS

Any discussion of the results to be expected from the special treatment of jaundiced patients designed to curb the abnormal bleeding must necessarily be divided chronologically in order that the various preoperative regimes may be properly evaluated.

Kehr (116) studied the compiled the statistics up to 1912 and reported that in cases of obstructive jaundice in which liver damage was acute and severe the expected postoperative mortality was approximately 75%; hemorrhage alone accounted for 42% of the total number of deaths. With the introduction of calcium chloride and more specific types of preoperative treatment, the incidence of bleeding has remained approximately the same but there has been a marked decrease in the postoperative mortality. In his discussion on preoperative care of jaundiced patients Ravdin divides the cases at the University of Pennsylvania Hospital since 1922 into three groups for comparison as to the treatment; effect on gross and effect on incidence of postoperative complications

peculiar to jaundiced patients. Group 1. includes 59 patients from 1922 to 1929. This group received calcium chloride and small amounts of glucose by vein before operation; no effort was made to raise the carbohydrate intake in the diet. Preoperative transfusions were not employed and after operation, transfusions were only rarely resorted to unless the patient was in extremis. Biliary decompression was practically never done. Refeeding of bile was not constant and bilirubemia in general was not allowed to become constant or stable before operation; ether was the usual anaesthetic. Of this group 22% showed postoperative hemorrhage with a mortality from hemorrhage alone of 8.5%. Hemorrhage occurred as a contributing cause of death in a number of other cases raising the total mortality in which hemorrhage occurred to 69%.

Group 2 included patients from 1929 through 1933. The principal differences in treatment were intravenous glucose during both pre and post operative periods along with high carbohydrate diets; frequent Van den Bergh determinations until the bilirubemia was constant; refeeding of bile in those patients that drained excessively; only occasional blood transfusions

preoperatively, and occasional use of the decompression apparatus. The use of calcium was abandoned; ether and spinal anaesthesia were used about equally. In this group the incidence of postoperative hemorrhage was 19.1%; the mortality from hemorrhage alone was 4.2% and the gross mortality in which hemorrhage was a factor was 33%.

Group 3 included cases from 1933 to 1937. Intravenous glucose was given freely both pre and postoperatively; gradual decompression of the biliary tract after operation was used extensively, operation was delayed until the bilirubemia was constant; bile was refed routinely and transfusions were used quite frequently preoperatively. Spinal anaesthesia was employed most frequently. The incidence of postoperative hemorrhage was 18.4%. The mortality from hemorrhage alone was 2% and the mortality in which hemorrhage was an associated factor was 23%.

These studies would seem to indicate that the incidence of hemorrhage was not decreased materially by improved preoperative treatment, but the mortality from hemorrhage alone was markedly decreased.

In their study of vitamin D and its therapeutic value in obstructive jaundice, McNealy and his assoc-

iates (146) found that in 56 patients who received vitamin D before operation, the incidence of postoperative hemorrhage was 12.6% and mortality from hemorrhage was 3.6%. This is compared with the group of 26 patients used as controls in which the incidence of postoperative hemorrhage was 61%, and the mortality from hemorrhage 12%. Boys (35) and Johnson (105) have reported similar findings in much smaller series.

The series of cases reported of patients receiving preoperative vitamin K therapy is relatively small because of the short time the vitamin has been available for clinical work. Butt and his associates at the Mayo Clinic have reported the largest series to date. In twenty-eight patients that received concentrates of vitamin K and bile salts orally before and after surgery, only 11% bled post operatively, none seriously, and there were no deaths from hemorrhage. This is contrasted with the fourteen cases used as controls who received no concentrate of vitamin K or bile salts preoperatively, 64% of whom bled after surgery. Those of the control group who bled preoperatively were given large amounts of vitamin K by duodenal tube or T-tube and the bleeding was controlled

in every case. Reports of Ravdin (191) Boyce (32) and others (188) (214), although too small to be conclusive seem to corroborate the clinical findings of the Mayo Clinic group fully.

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